UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,769	10/20/2001	Randy D. McKinnon	268/260	5576

26259 7590 09/15/2004

LICATLA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053

EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/051,769	MCKINNON, RANDY D.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/26/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Exhibits A-E*

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I, claims 1-4, and 6-9 in the reply filed on 06/25/04 is acknowledged. The traversal is on the ground(s) that the restriction requirement of record does not meet the two criteria set out in MPEP § 803. The inventions have not been shown to be independent and distinct and the examination of all groups would not impose a serious burden on the examiner. This is not found persuasive.

MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the two groups are distinct for the reasons set forth in Paper mailed on 06/02/2004. As to the question of burden of search, the inventions are classified differently, necessitating different searches in the US Patent class/subclass. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. In the instant case, the search for the polynucleotides and the method of detecting whether a patient is at risk for progression into glioblastoma multiforme using a polynucleotide are not coextensive. The search for group II would require a text search for the method of detecting whether a patient is at risk for progression into glioblastoma multiforme in addition to the nucleic acid product search. Prior art, which teaches the claimed polynucleotides, would not necessarily be applicable to the method of using the claimed polynucleotides for detecting whether a

patient is at risk for progression into glioblastoma multiforme. Moreover, even if the polynucleotide product were known, the method of diagnosis using the product may be novel and unobvious in view of the preamble or active steps. Different searches and issues are involved in the examination of each group.

The requirement is still deemed proper and is therefore made FINAL.

Claim 5 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 06/25/04.

Claims 1-9 are pending. Claims 1-4, and 6-9 are examined on merits.

Specification

The disclosure at pages 2, 12, and 14 of the specification is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The specification is also objected for the following reason: The "stringent conditions" are considered essential subject matter to the instant application and the claimed invention.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference (i.e. McKinnon et al., note page 5, line 11 of the specification). The amendment must be accompanied

by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112; however this does not bar incorporation by reference. Ex parte Schwarze, 151 USPQ 426 (Bd. of Appeals, 1966). An application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an allowed U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. 112). "Essential material" may not be incorporated by reference to (1) patents or applications published by foreign countries or regional patent offices, to (2) non-patent publications, to (3) a U.S. patent or application which itself incorporates "essential material" by reference or to (4) a foreign application. See In re Fouche, 169 USPQ 429; 439 F.2d 1237 (CCPA 1971).

Nonessential subject matter may be incorporated by reference to (1) patents or application published by the United states or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications or (3) non-patent publications, for purposes of indicating the background of the invention or illustrating the state of the art.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This written description rejection is made because the claims are interpreted as drawn to a genus i.e. any nucleic acid that minimally contains SEQ ID NO:2, or a sequence that hybridizes to SEQ ID NO:2 under stringent conditions.

The applicable standard for the written description requirement can be found: MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Prove Inc., 63 USPQ2d 1609; Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111; and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC 2004).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

The specification discloses that instant SEQ IDNO:2 is an EST. The present claims with the open transitional phrase "comprising" an EST encompass full-length genes and cDNAs that are not further described. There is a substantial variability among the species of cDNAs encompassed within the scope of the claims because SEQ ID NO:2 is only a fragment of any full-length gene(s) or cDNA species. They are structurally unrelated. A description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequences, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. A nucleic acid hybridizes to SEQ ID NO:2 or its complement also fails to provide adequate written description and evidence of possession of a claimed genus. The present claims do not identify a function associated with the partial structure of SEQ ID NO:2 or hybridizing molecules. Since the breath of the claims as reading on genes yet to be discovered, the lack of correlation between the claimed structure and the function of the genes, it is concluded that the written description requirement is not satisfied

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the

encompassed genus of nucleic acid molecules, given that the specification has only described SEQ ID NO: 2. Therefore, only isolated nucleic acid consisting of SEQ ID NO:2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Claims 1-4, and 6-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the claimed invention is interpreted as drawn to an isolated nucleic acid molecule comprising SEQ ID NO:2 or kit containing two primers i.e. SEQ ID NO:5, and 6 for use in detection of whether a patient is at risk for progression into glioblastoma multiforme, or other malignant phenotype.

The specification teaches that SEQ ID NO:2 is an EST sequence. The specification asserts that the claimed SEQ ID NO:2 and the two primers i.e. SEQ ID NOs:5, and 6 could be used in detection of whether a patient is at risk for progression into glioblastoma multiforme, or other malignant phenotype. The specification discloses that the claimed nucleic acid is expressed at high level in immortal glioblast cell lines. However, the specification does not disclose whether the claimed nucleic acid is overexpressed or underexpressed in glioblastoma multiforme tissue compared to the healthy tissue control. Since the nucleic acid is expressed at higher level in normal brain tissues, it is not clear how to use the claimed invention to evaluate whether a patient is at risk for progression into glioblastoma multiforme.

The amount of direction or guidance by the inventor how to use the claimed invention is limited. The quantity of experimentation needed to use the claimed invention is large. In order to use the claimed invention, one skilled in the art has to screen a large quantity of clinical samples to determine whether a differential SEQ ID NO:2 expression is correlated with glioblastoma multiforme, or other malignant phenotype.

Cancer diagnosis and prognosis art using a new marker is unpredictable. Since the specification does not discloses that an altered levels or forms of the claimed nucleic acid is associated with glioblastoma multiforme, or other malignant phenotype in vivo as compared with the corresponding healthy tissue, one of skill in the art would have reason to doubt that the instantly claimed SEQ ID NO:2, 5, and 6 could be used in a method of identifying a patient at risk for progression into the malignant phenotype, or

glioblastoma mutiforme. McKinnon et al. (IDS AP filed on 03/26/2002, J. Cell Biology, vol. 85, pages 890-902) at the last sentence of abstract teach that a marker expression of in vitro cells such as immortalized cultured cells may not be a very useful indicator of what the expression pattern would be in the counter-part in vivo cells because the tight regulation of expression is lost in cells in culture.

Tockman et al., (Cancer Res., 1992, 52:2711s-2718s) teach that cancer diagnosis or prognosis is an unpredictable art. The specification does not provide in vivo data that a patient at risk of progression into glioblatoma multiforme has an altered expression of the claimed nucleic acid. Tockman et al., teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to the instant invention. Tockman et al teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of tumorigenicity have clear biological plausibility as markers of preclinical cancer and if validated can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with

subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Likewise, Fujisawa et al., (American Journal of Pathology, vol. 155, pages 387-394) teach a new marker for glioblatoma (a malignant type of brain tumor) phenotype detection has to be validated against acknowledged disease end points. Fujisawa et al., teach that in order to use a new marker for detection of glioblastoma, it is necessary to examine the clinical samples from patients who have glioblastoma.

Since the instant specification does not teach any differential expression or a mutated form of the instantly claimed nucleic acid in patients with glioblastoma or any other malignant phenotype, one of skill in the art has to screen a large quantity of clinical samples from brain tumor patients. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

Considering the unpredictable state of art, limited guidance, no examples in the specification how to use the instantly claimed invention, it is concluded that undue experimentation is required to practice the invention.

Further, claim 2 is rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure, which is not enabling. The limitation "under stringent condition" critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). In order to practice the invention claimed in claim 2, one of skill has to know the claimed stringent conditions incorporated by reference. Note the objection to the specification above. An amendment accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application would obviate this part of rejection. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 3 is rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter. Claim 3, as written, does not sufficiently distinguish over nucleic acids as they exist naturally because the claim does not particularly point out any non-naturally occurring differences between the claimed product and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*,

447 U.S. 303, 206 USPQ 193 (1980). The claim should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified". See MPEP 2105.

Claims 1-4, and 6-9 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well-established utility.

The disclosed utilities for the claimed nucleic acids are to diagnose and treat brain cancer including glioblastoma (note the paragraph bridging pages 2 and 3 of the specification).

The specification discloses that the claimed nucleic acid is expressed at high level in immortal glioblast cell lines, as well as brain cortex, liver, thymus, or kidney cells, while expressed at lower levels in testis. Since the specification does not disclose that the claimed nucleic acid is over-expressed in in vivo glioblastoma or any other in vivo brain tumors, the asserted use of the claimed invention in diagnosis of brain tumor including glioblastoma is not substantial. The specification does not disclose whether the claimed nucleic acid is overexpressed or underexpressed in a specific, diseased tissue compared to the healthy tissue control.

The overexpression in immortal glioblast cell lines is not considered to be substantial either because this disclosure does not lead to substantial use of the claimed invention in diagnosis of a brain tumor. The art acknowledges that the characteristics of cultured cell lines generally differ significantly from the characteristics of in vivo primary cancers or metastatic cancers. Freshney (Culture of Animal Cells, A

Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years.

The specification discloses that the instantly claimed nucleic acid encodes a protein that shares sequence homology with a gene product of Drosophila (page 3). However, the art generally acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Scott et al (Nature

Genetics, 1999, 21:440-443) teach that the function of newly identified gene products is unpredictable even when the database searches reveal significant homology to proteins of known function. Scott et al teaches that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. states that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi

functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247:1306-1310) state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306). Thus, the specification fails to support the asserted credible, specific and substantial utility of the newly identified instantly claimed nucleic acids.

In Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), the court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §

101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The instant claims are drawn to nucleic acid, which has undetermined function or biological significance. Until some actual and specific activity can be attributed to the claimed nucleic acids, the claimed invention is incomplete.

Claims 1-4, and 6-9 also are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 6, and 7 are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,673,549 (06 January 2004, with the effective filing date of 12 October 2000).

Claims 1-4, 6, and 7 are interpreted as drawn to an isolated nucleic acid comprising SEQ ID NO:2 (or comprising a sequence hybridizes to the complement of

SEQ ID NO:2), wherein said nucleic acid is labeled with various art-known labels (claim 4), wherein said nucleic acid is in a kit with instruction for use (claims 6, and 7).

US 6,673,549 in claim 1 teaches an isolated nucleic acid i.e. SEQ ID NO: 899 comprising instant SEQ ID NO:2 (comprising a sequence hybridizes to the complement of SEQ ID NO:2). Note Exhibit A (sequence alignment). US 6,673,549 also teaches that the nucleic acid is in a kit i.e. a microarray (note column 28). According to Merriam-Webster online dictionary downloaded on 8/16/04 from url>>>www.m-w.com, "kit" is defined as collection of articles. Thus, the nucleic acid comprising instant SEQ ID NO:2 in the collections of cDNA in a microarray is in a kit. Further, US 6,673,549 teaches how to use the nucleic acid in cDNA microarry for expression profiling purposes and other instructions for uses at columns 14 to 17. US 6,673,549 teaches various reagents including radioisotope and other labels, and other components in performing assays at columns 13-17. As for claims 3, 4, 6, and 7, the preamble recitation of use in identifying a patient at risk for progression into the malignant phenotype or detecting whether a patient is at risk for progression into glioblastoma multiforme is merely suggestive of an intended use and is not given patentable weight for purposes of comparing the claims with the prior art. The claims read on the nucleic acid *per se*.

Claims 1-3 are rejected under 35 U.S.C. 102(a) as being anticipated by GenBank accession number AC005887 (05 November 1999).

Claims 1-3 are interpreted as drawn to an isolated nucleic acid comprising SEQ ID NO:2.

GenBank accession number AC005887 teaches an isolated nucleic acid that matches 100 % to instant SEQ ID NO:2. Note the attached Exhibit B (sequence alignment). As for claim 2, since GenBank accession number AC005887 matches 100 % to the instant SEQ ID NO:2, it would hybridizes to the complement of SEQ ID NO:2. As for claim 3, the preamble recitation of use in identifying a patient at risk for progression into the malignant phenotype is merely suggestive of an intended use and is not given patentable weight for purposes of comparing the claim with the prior art. The claim reads on the nucleic acid *per se*.

Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by either US 5,759,811 (02 June 1998) or GenBank Acc. No AW013379 (10 September 1999).

Claim 2 is drawn to a nucleic acid comprising a sequence hybridizes to the complement of SEQ ID NO:2.

US 5,759,811 teaches SEQ ID NO:5 at columns 21-24, and claims 4, and 16, wherein nucleotides #988 to 1008 of SEQ ID NO:5 (total 21 nucleotides) match 100 % with nucleotides # 139 to #159 of the instant SEQ ID NO:2. See Exhibit D (sequence alignment).

GenBank Acc. No AW013379 teaches a nucleic acid molecule that matches 100 % to the nucleotides #1 to 42 of the instant SEQ ID NO:2. See Exhibit E (sequence alignment).

Since the art teaches nucleic acid molecules comprising either 21 or 42 contiguous nucleotides of instant SEQ ID NO:2, it is the Office's position that the nucleic

acid of art would hybridizes to the complement of instant SEQ ID NO:2. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the two nucleic acid molecules of the prior art do not hybridize to complement of SEQ ID NO:2. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed nucleic acid is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, and 6-9 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15, 17-23, 25, 26, 37, and 38 of copending Application No. 10/224,624. Although the conflicting claims are not identical, they are not patentably distinct from each other because SEQ ID NO:7 in claim 1 of the copending application anticipates instant claim

1. Note Exhibit C (sequence alignment). This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey C Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642

GenCore version 5.1.6

OM nucleic - nucleic search, using sw model

Run on: July 18, 2004, 12:32:20 ; Search time 88.141 Seconds
(without alignments)
1643.301 Million cell updates/sec

Title: US-10-051-769-2
Perfect score: 261
Sequence: 1 gatcaaggtggagttcgagg.....cacctggccatcgacgtgga 261

Scoring table: IDENTITY_NUC
Gapop 10.0 , Gapext 1.0

Searched: 682709 seqs, 277475446 residues

Total number of hits satisfying chosen parameters: 1365418

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : Issued_Patents_NA:*
1: /cgn2_6/ptodata/2/ina/5A_COMB.seq:*
2: /cgn2_6/ptodata/2/ina/5B_COMB.seq:*
3: /cgn2_6/ptodata/2/ina/6A_COMB.seq:*
4: /cgn2_6/ptodata/2/ina/6B_COMB.seq:*
5: /cgn2_6/ptodata/2/ina/PCTUS_COMB.seq:*
6: /cgn2_6/ptodata/2/ina/backfiles1.seq:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

	Result No.	Score	% Query Match	Length	DB	ID	Description
	1	261	100.0	4303	4	US-09-976-594-899	Sequence 899, App
	2	51.6	19.8	6436	4	US-09-600-099-1	Sequence 1, Appli
c	3	44.4	17.0	450	4	US-09-252-991A-8011	Sequence 8011, Ap
	4	44.4	17.0	1467	4	US-09-252-991A-8188	Sequence 8188, Ap
c	5	44.4	17.0	2823	4	US-09-252-991A-8068	Sequence 8068, Ap
	6	44.4	17.0	2949	4	US-09-252-991A-8249	Sequence 8249, Ap
	7	44.4	17.0	23673	4	US-09-773-816-1	Sequence 1, Appli
	8	43.6	16.7	4849	4	US-09-620-312D-39	Sequence 39, Appl
	9	43.4	16.6	4403765	3	US-09-103-840A-2	Sequence 2, Appli
	10	43.4	16.6	4411529	3	US-09-103-840A-1	Sequence 1, Appli
	11	43.2	16.6	2825	4	US-09-196-390-5	Sequence 5, Appli
c	12	42.4	16.2	77536	4	US-09-410-551B-1	Sequence 1, Appli
c	13	42.2	16.2	450	4	US-09-252-991A-10221	Sequence 10221, A
c	14	42.2	16.2	561	4	US-09-252-991A-10438	Sequence 10438, A
c	15	42.2	16.2	705	4	US-09-252-991A-10340	Sequence 10340, A
c	16	42.2	16.2	1053	4	US-09-252-991A-13541	Sequence 13541, A
	17	42.2	16.2	1167	4	US-09-252-991A-10810	Sequence 10810, A
	18	42.2	16.2	1557	4	US-09-252-991A-13907	Sequence 13907, A
	19	42.2	16.2	1722	4	US-09-252-991A-13800	Sequence 13800, A
	20	41.8	16.0	3937	4	US-10-164-595-7	Sequence 7, Appli
	21	41.6	15.9	1910	3	US-09-593-711A-3	Sequence 3, Appli
	22	41.6	15.9	1914	1	US-07-601-094-1	Sequence 1, Appli
	23	41.6	15.9	1914	1	US-08-012-735-1	Sequence 1, Appli
	24	41.4	15.9	1194	4	US-09-252-991A-11352	Sequence 11352, A
c	25	41.4	15.9	1500	4	US-09-252-991A-11312	Sequence 11312, A
	26	41.4	15.9	2618	4	US-09-857-556A-25	Sequence 25, Appl
	27	41	15.7	1398	4	US-09-252-991A-14375	Sequence 14375, A
c	28	41	15.7	1416	4	US-09-252-991A-14328	Sequence 14328, A
	29	40.8	15.6	942	2	US-08-446-806-2	Sequence 2, Appli
	30	40.8	15.6	942	3	US-09-385-028-17	Sequence 17, Appl
	31	40.8	15.6	942	4	US-09-726-614-17	Sequence 17, Appl
	32	40.8	15.6	942	4	US-09-385-040-17	Sequence 17, Appl
c	33	40.8	15.6	1218	4	US-09-252-991A-7267	Sequence 7267, Ap
	34	40.8	15.6	11604	3	US-09-385-028-13	Sequence 13, Appl
	35	40.8	15.6	11604	4	US-09-726-614-13	Sequence 13, Appl
	36	40.8	15.6	11604	4	US-09-385-040-13	Sequence 13, Appl
	37	40.8	15.6	15079	3	US-09-385-028-1	Sequence 1, Appli
	38	40.8	15.6	15079	4	US-09-726-614-1	Sequence 1, Appli
	39	40.8	15.6	15120	4	US-09-385-040-1	Sequence 1, Appli
	40	40.4	15.5	513	4	US-09-252-991A-9735	Sequence 9735, Ap
c	41	40.4	15.5	858	4	US-09-252-991A-9510	Sequence 9510, Ap
	42	40.4	15.5	918	4	US-09-252-991A-9653	Sequence 9653, Ap
	43	40.4	15.5	1062	4	US-09-252-991A-9694	Sequence 9694, Ap
	44	40.4	15.5	1953	4	US-09-252-991A-5663	Sequence 5663, Ap
c	45	40.4	15.5	2721	4	US-09-252-991A-5561	Sequence 5561, Ap

ALIGNMENTS

RESULT 1
US-09-976-594-899
; Sequence 899, Application US/09976594
; Patent No. 6673549
; GENERAL INFORMATION:
; APPLICANT: Furness, Michael
; APPLICANT: Buchbinder, Jenny
; TITLE OF INVENTION: GENES EXPRESSED IN C3A LIVER CELL CULTURES TREATED WITH STEROIDS
; FILE REFERENCE: PA-0041 US
; CURRENT APPLICATION NUMBER: US/09/976,594
; CURRENT FILING DATE: 2001-10-12
; PRIOR APPLICATION NUMBER: 60/240,409
; PRIOR FILING DATE: 2000-10-12
; NUMBER OF SEQ ID NOS: 1143
; SOFTWARE: PERL Program
; SEQ ID NO 899
; LENGTH: [redacted]03
; TYPE: DNA
; ORGANISM: Homo sapiens
; FEATURE:
; NAME/KEY: misc_feature
; OTHER INFORMATION: Incyte ID No. 6673549 225420.1
US-09-976-594-899

Query Match 100.0%; Score 261; DB 4; Length 4303;
Best Local Similarity 100.0%; Pred. No. 5.5e-48;
Matches 261; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         79 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 138

Qy         61 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        139 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 198

Qy        121 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        199 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 258

Qy        181 GCCCGCCGCCTGCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        259 GCCCGCCGCCTGCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 318

Qy        241 CCACCTGGCCATCGACGTGGA 261
              |||||||||||||||||||||
Db        319 CCACCTGGCCATCGACGTGGA 339
```

RESULT 2

```
                     ZO-1/2. Also called DHR (Dlg homologous region) or GLGF
                     (relatively well conserved tetrapeptide in these domains).
                     Some PDZs have been shown to bind C-terminal polypeptides"
                     /db_xref="CDD:smart00228"
     misc_feature    2723. .2851
                     /note="DAG_PE-bind; Region: Phorbol esters/diacylglycerol
                     binding domain (C1 domain). This domain is also known as
                     the Protein kinase C conserved region 1 (C1) domain"
                     /db_xref="CDD:pfam00130"
ORIGIN

  Query Match           100.0%;  Score 261;  DB 9;  Length 3856;
  Best Local Similarity  100.0%;  Pred. No. 1e-120;
  Matches  261;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        568 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 627

Qy         61 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        628 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 687

Qy        121 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        688 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 747

Qy        181 GCCCGCCGCCTGCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        748 GCCCGCCGCCTGCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 807

Qy        241 CCACCTGGCCATCGACGTGGA 261
              |||||||||||||||||||||
Db        808 CCACCTGGCCATCGACGTGGA 828


RESULT 5
AL359836/c
LOCUS       AL359836               49052 bp    DNA     linear   PRI 21-DEC-2001
DEFINITION  Human DNA sequence from clone RP11-389E6 on chromosome 10, complete
            sequence.
ACCESSION   AL359836
VERSION     AL359836.16  GI:17977720
KEYWORDS    HTG.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 49052)
  AUTHORS   Smith,M.
  TITLE     Direct Submission
  JOURNAL   Submitted (21-DEC-2001) Wellcome Trust Sanger Institute, Hinxton,
            Cambridgeshire, CB10 1SA, UK. E-mail enquiries:
            humquery@sanger.ac.uk Clone requests: clonerequest@sanger.ac.uk
COMMENT     On Dec 23, 2001 this sequence version replaced gi:17384082.
            During sequence assembly data is compared from overlapping clones.
            Where differences are found these are annotated as variations
            together with a note of the overlapping clone name. Note that the
            variation annotation may not be found in the sequence submission
            corresponding to the overlapping clone, as we submit sequences with
            only a small overlap as described above.
            This sequence was finished as follows unless otherwise noted: all
            regions were either double-stranded or sequenced with an alternate
            chemistry or covered by high quality data (i.e., phred quality >=
            30); an attempt was made to resolve all sequencing problems, such
            as compressions and repeats; all regions were covered by at least
            one plasmid subclone or more than one M13 subclone; and the
            assembly was confirmed by restriction digest. The following
            abbreviations are used to associate primary accession numbers given
            in the feature table with their source databases: Em:, EMBL; Sw:,
            SWISSPROT; Tr:, TREMBL; Wp:, WORMPEP; Information on the WORMPEP
            database can be found at
            http://www.sanger.ac.uk/Projects/C_elegans/wormpep This sequence
            was generated from part of bacterial clone contigs of human
            chromosome 10, constructed by the Sanger Centre Chromosome 10
            Mapping Group.  Further information can be found at
            http://www.sanger.ac.uk/HGP/Chr10
            RP11-389E6 is from the library RPCI-11.2 constructed by the group
            of Pieter de Jong. For further details see
            http://www.chori.org/bacpac/home.htm
            VECTOR: pBACe3.6
            IMPORTANT: This sequence is not the entire insert of clone
            RP11-389E6 It may be shorter because we sequence overlapping
            sections only once, except for a short overlap.
            The true left end of clone CTA-109P11 is at 47053 in this sequence.
            The true right end of clone RP11-129M16 is at 2000 in this
            sequence.
FEATURES    Location/Qualifiers
     source 1. .49052
            /organism="Homo sapiens"
            /mol_type="genomic DNA"
            /db_xref="taxon:9606"
            /chromosome="10"
            /clone="RP11-389E6"
            /clone_lib="RPCI-11.2"
ORIGIN

  Query Match           100.0%;  Score 261;  DB 9;  Length 49052;
  Best Local Similarity  100.0%;  Pred. No. 8.4e-121;
  Matches  261;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      29767 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 29708

Qy         61 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      29707 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 29648

Qy        121 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      29647 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 29588

Qy        181 GCCCGCCGCCTGCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      29587 GCCCGCCGCCTGCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 29528

Qy        241 CCACCTGGCCATCGACGTGGA 261
              |||||||||||||||||||||
Db      29527 CCACCTGGCCATCGACGTGGA 29507


RESULT 6
AC005887
LOCUS       AC005887               120578 bp    DNA     linear   PRI 05-NOV-1999
DEFINITION  citb_173_i_12, complete sequence.
ACCESSION   AC005887
VERSION     AC005887.3  GI:6249675
KEYWORDS    HTG.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 120578)
  AUTHORS   Smith,D.R.
  TITLE     Sequencing of Human Chromosome 10
  JOURNAL   Unpublished
REFERENCE   2  (bases 1 to 120578)
  AUTHORS   Smith,D.R.
  TITLE     Direct Submission
  JOURNAL   Submitted (29-OCT-1998) Genome Therapeutics Corporation, 100 Beaver
            Street, Waltham, MA 02154, USA
REFERENCE   3  (bases 1 to 120578)
  AUTHORS   Smith,D.R.
  TITLE     Direct Submission
  JOURNAL   Submitted (11-DEC-1998) Genome Therapeutics Corporation, 100 Beaver
```

Street, Waltham, MA 02154, USA
REFERENCE 4 (bases 1 to 120578)
AUTHORS Smith,D.R.
TITLE Direct Submission
JOURNAL Submitted (02-MAR-1999) Genome Therapeutics Corporation, 100 Beaver Street, Waltham, MA 02154, USA
REFERENCE 5 (bases 1 to 120578)
AUTHORS Smith,D.R.
TITLE Direct Submission
JOURNAL Submitted (05-NOV-1999) Genome Therapeutics Corporation, 100 Beaver Street, Waltham, MA 02154, USA
REMARK Vector Sequence Clipped
COMMENT On Nov 5, 1999 this sequence version replaced gi:4314331.
FEATURES Location/Qualifiers
source 1. .120578
/organism="Homo sapiens"
/mol_type="genomic DNA"
/db_xref="taxon:9606"
/chromosome="10"
/map="10q25"
/clone_lib="CIT987SK-1173I12"
ORIGIN

Query Match 100.0%; Score 261; DB 9; Length 120578;
Best Local Similarity 100.0%; Pred. No. 7.8e-121;
Matches 261; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      53976 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 54035

Qy         61 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      54036 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 54095

Qy        121 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      54096 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 54155

Qy        181 GCCCGCCGCCTGCCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      54156 GCCCGCCGCCTGCCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 54215

Qy        241 CCACCTGGCCATCGACGTGGA 261
              |||||||||||||||||||||
Db      54216 CCACCTGGCCATCGACGTGGA 54236
```

RESULT 7
BD169701
LOCUS BD169701 3847 bp DNA linear PAT 17-JAN-2003
DEFINITION Human glioma antigen and method of preparing the same.
ACCESSION BD169701
VERSION BD169701.1 GI:27875513
KEYWORDS WO 02055695-A/6.
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (bases 1 to 3847)
AUTHORS Toda,M., Kawakami,Y., Kawase,T. and Iizuka,Y.
TITLE Human glioma antigen and method of preparing the same
JOURNAL Patent: WO 02055695-A 6 18-JUL-2002;
KEIO UNIVERSITY,MASAHIRO TODA,YUTAKA KAWAKAMI,TAKESHI KAWASE, YUKIHIKO IIZUKA
COMMENT OS Homo sapiens (human)
PN WO 02055695-A/6
PD 18-JUL-2002
PF 30-NOV-2001 WO 2001JP010505
PR 09-JAN-2001 JP 01P 001965
PI MASAHIRO TODA,YUTAKA KAWAKAMI,TAKESHI KAWASE,YUKIHIKO IIZUKA
PC C12N15/12,C12N5/10,A01K67/027,A61K31/711,A61K38/00,A61K39/00,
PC A61K39/395,
PC A61K45/00,A61K48/00,A61P35/00,C07K14/47,C07K16/18,C07K19/00,
PC C12Q1/02,
PC C12Q1/68
CC Human glioma antigen and method of preparing the same FH Key Location/Qualifiers
FT CDS (211). .(2883).
FEATURES Location/Qualifiers
source 1. .3847
/organism="Homo sapiens"
/mol_type="genomic DNA"
/db_xref="taxon:9606"
ORIGIN

Query Match 18.0%; Score 47; DB 6; Length 3847;
Best Local Similarity 100.0%; Pred. No. 1e-12;
Matches 47; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy        215 GCGGAGGTGGAGTACAACGGGGGCTTCCACCTGGCCATCGACGTGGA 261
              ||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 GCGGAGGTGGAGTACAACGGGGGCTTCCACCTGGCCATCGACGTGGA 47
```

RESULT 8
AC108407/c
LOCUS AC108407 68196 bp DNA linear HTG 27-JAN-2002
DEFINITION Mus musculus clone RP24-422P10, LOW-PASS SEQUENCE SAMPLING.
ACCESSION AC108407
VERSION AC108407.1 GI:18377216
KEYWORDS HTG; HTGS_PHASE0.
SOURCE Mus musculus (house mouse)
ORGANISM Mus musculus
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
REFERENCE 1 (bases 1 to 68196)
AUTHORS Birren,B., Linton,L., Nusbaum,C. and Lander,E.
TITLE Mus musculus, clone RP24-422P10
JOURNAL Unpublished
REFERENCE 2 (bases 1 to 68196)
AUTHORS Birren,B., Linton,L., Nusbaum,C., Lander,E., Ali,A., Allen,N., Anderson,S., Barna,N., Bastien,V., Boguslavkiy,L., Boukhgalter,B., Brown,A., Camarata,J., Campopiano,A., Chang,J., Chazaro,B., Choepel,Y., Colangelo,M., Collins,S., Collymore,A., Cook,A., Cooke,P., DeArellano,K., Dewar,K., Diaz,J.S., Dodge,S., Faro,S., Ferreira,P., FitzHugh,W., Gage,D., Galagan,J., Gardyna,S., Ginde,S., Gord,S., Goyette,M., Graham,L., Grand-Pierre,N., Hagos,B., Horton,L., Hulme,W., Iliev,I., Johnson,R., Jones,C., Kamat,A., Karatas,A., Kells,C., LaRocque,K., Lamazares,R., Landers,T., Lehoczky,J., Levine,R., Liu,G., MacLean,C., Macdonald,P., Major,J., Marquis,N., Matthews,C., McCarthy,M., McEwan,P., McKernan,K., Meldrim,J., Meneus,L., Mihova,T., Mlenga,V., Murphy,T., Naylor,J., Nguyen,C., Nicol,R., Norbu,C., Norman,C.H., O'Connor,T., O'Donnell,P., O'Neil,D., Oliver,J., Peterson,K., Phunkhang,P., Pierre,N., Pollara,V., Raymond,C., Retta,R., Rieback,M., Riley,R., Rise,C., Rogov,P., Roman,J., Rosetti,M., Roy,A., Santos,R., Schauer,S., Schupback,R., Seaman,S., Severy,P., Spencer,B., Stange-Thomann,N., Stojanovic,N., Strauss,N., Subramanian,A., Talamas,J., Tesfaye,S., Theodore,J., Topham,K., Travers,M., Travis,N., Trigilio,J., Vassiliev,H., Viel,R., Vo,A., Wilson,B., Wu,X., Wyman,D., Ye,W.J., Young,G., Zainoun,J., Zembek,L., Zimmer,A. and Zody,M.
TITLE Direct Submission
JOURNAL Submitted (27-JAN-2002) Whitehead Institute/MIT Center for Genome Research, 320 Charles Street, Cambridge, MA 02141, USA
COMMENT All repeats were identified using RepeatMasker:
Smit, A.F.A. & Green, P. (1996-1997)
http://ftp.genome.washington.edu/RM/RepeatMasker.html
-------------- Genome Center
Center: Whitehead Institute/ MIT Center for Genome Research
Center code: WIBR
Web site: http://www-seq.wi.mit.edu
Contact: sequence_submissions@genome.wi.mit.edu
-------------- Project Information
Center project name: L18881

```
;  CURRENT APPLICATION NUMBER: US/10/224,624
;  CURRENT FILING DATE:  2002-08-20
;  PRIOR APPLICATION NUMBER: 60/242,160
;  PRIOR FILING DATE: 2000-10-20
;  PRIOR APPLICATION NUMBER: 10/051,769
;  PRIOR FILING DATE: 2001-10-20
;  NUMBER OF SEQ ID NOS: 9
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 9
;   LENGTH: 3465
;   TYPE: DNA
;   ORGANISM: Homo sapiens
US-10-224-624-9

  Query Match           100.0%;  Score 261;  DB 15;  Length 3465;
  Best Local Similarity  100.0%;  Pred. No. 2.6e-58;
  Matches  261;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        366 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 425

Qy         61 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        426 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 485

Qy        121 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        486 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 545

Qy        181 GCCCGCCGCCTGCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        546 GCCCGCCGCCTGCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 605

Qy        241 CCACCTGGCCATCGACGTGGA 261
              |||||||||||||||||||||
Db        606 CCACCTGGCCATCGACGTGGA 626


RESULT 9
US-10-112-944-63
; Sequence 63, Application US/10112944
; Publication No. US20040048249A1
; GENERAL INFORMATION:
;  APPLICANT: Tang, Y. Tom
;  APPLICANT:  Yang, Yonghong
;  APPLICANT:  Weng, Gezhi
;  APPLICANT:  Zhang, Jie
;  APPLICANT:  Ren, Feiyan
;  APPLICANT:  Xue, Aidong J.
;  APPLICANT:  Wang, Jian-Rui
;  APPLICANT:  Wehrman, Tom
;  APPLICANT:  Ghosh, Malabika
;  APPLICANT:  Wang, Dunrui
;  APPLICANT:  Zhao, Qing A.
;  APPLICANT:  Wang, Zhiwei
;  TITLE OF INVENTION: No. US20040048249A1el Nucleic Acids and
;  TITLE OF INVENTION:  Secreted Polypeptides
;  FILE REFERENCE: 805A
;  CURRENT APPLICATION NUMBER: US/10/112,944
;  CURRENT FILING DATE:  2002-03-28
;  PRIOR APPLICATION NUMBER: US 09/488,725
;  PRIOR FILING DATE: 2000-01-21
;  PRIOR APPLICATION NUMBER: US 09/491,404
;  PRIOR FILING DATE: 2000-01-25
;  PRIOR APPLICATION NUMBER: US 09/496,914
;  PRIOR FILING DATE: 2000-02-03
;  PRIOR APPLICATION NUMBER: US 09/515,126
;  PRIOR FILING DATE: 2000-02-28
;  PRIOR APPLICATION NUMBER: US 09/519,705
;  PRIOR FILING DATE: 2000-03-07
;  PRIOR APPLICATION NUMBER: US 09/540,217
;  PRIOR FILING DATE: 2000-03-31
;  PRIOR APPLICATION NUMBER: US 09/552,929
;  PRIOR FILING DATE: 2000-04-18
;  PRIOR APPLICATION NUMBER: US 09/577,408
;  PRIOR FILING DATE: 2000-05-18
;  NUMBER OF SEQ ID NOS: 924
;  SOFTWARE: pt_FL_genes Version 5.0
; SEQ ID NO 63
;   LENGTH: 3649
;   TYPE: DNA
;   ORGANISM: Homo sapiens
;   FEATURE:
;   NAME/KEY: CDS
;   LOCATION: (1)..(3462)
US-10-112-944-63

  Query Match           100.0%;  Score 261;  DB 13;  Length 3649;
  Best Local Similarity  100.0%;  Pred. No. 2.6e-58;
  Matches  261;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        366 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 425

Qy         61 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        426 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 485

Qy        121 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        486 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 545

Qy        181 GCCCGCCGCCTGCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        546 GCCCGCCGCCTGCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 605

Qy        241 CCACCTGGCCATCGACGTGGA 261
              |||||||||||||||||||||
Db        606 CCACCTGGCCATCGACGTGGA 626


RESULT 10
US-10-224-624-7
; Sequence 7, Application US/10224624
; Publication No. US20030108915A1
; GENERAL INFORMATION:
;  APPLICANT: McKINNON, Randall D.
;  TITLE OF INVENTION: Glioblastoma Multiforme Associated Protein GliTEN
;  FILE REFERENCE: 54704.8059.US00
;  CURRENT APPLICATION NUMBER: US/10/224,624
;  CURRENT FILING DATE:  2002-08-20
;  PRIOR APPLICATION NUMBER: 60/242,160
;  PRIOR FILING DATE: 2000-10-20
;  PRIOR APPLICATION NUMBER: 10/051,769
;  PRIOR FILING DATE: 2001-10-20
;  NUMBER OF SEQ ID NOS: 9
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 7
;   LENGTH: 3832
;   TYPE: DNA
;   ORGANISM: Homo sapiens
;   FEATURE:
;   NAME/KEY: CDS
;   LOCATION: (178)..(3639)
;   OTHER INFORMATION:
US-10-224-624-7

  Query Match           100.0%;  Score 261;  DB 15;  Length 3832;
  Best Local Similarity  100.0%;  Pred. No. 2.6e-58;
  Matches  261;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        543 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 602
```

Exhibit C Page 2 of 2

```
Qy          61 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 120
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         603 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 662

Qy         121 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 180
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         663 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 722

Qy         181 GCCCGCCGCCTGCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 240
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         723 GCCCGCCGCCTGCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 782

Qy         241 CCACCTGGCCATCGACGTGGA 261
               |||||||||||||||||||||
Db         783 CCACCTGGCCATCGACGTGGA 803
```

```
RESULT 11
US-10-276-774-950
; Sequence 950, Application US/10276774
; Publication No. US20040053245A1
; GENERAL INFORMATION:
;  APPLICANT: Hyseq, Inc.
;  APPLICANT:  Tang, Y, Tom et al
;  TITLE OF INVENTION: No. US20040053245Alel Nucleic Acids and Polypeptides
;  FILE REFERENCE: 21272-030
;  CURRENT APPLICATION NUMBER: US/10/276,774
;  CURRENT FILING DATE:  2002-11-18
;  PRIOR APPLICATION NUMBER: 09/560,875
;  PRIOR FILING DATE: 2000-04-27
;  PRIOR APPLICATION NUMBER: 09/496,914
;  PRIOR FILING DATE: 2000-02-03
;  NUMBER OF SEQ ID NOS: 2700
;  SOFTWARE: Custom
; SEQ ID NO 950
;   LENGTH: 4470
;   TYPE: DNA
;   ORGANISM: Homo sapiens
US-10-276-774-950

  Query Match             100.0%;  Score 261;  DB 13;  Length 4470;
  Best Local Similarity   100.0%;  Pred. No. 2.5e-58;
  Matches  261;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy           1 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 60
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         366 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 425

Qy          61 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 120
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         426 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 485

Qy         121 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 180
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         486 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 545

Qy         181 GCCCGCCGCCTGCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 240
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         546 GCCCGCCGCCTGCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 605

Qy         241 CCACCTGGCCATCGACGTGGA 261
               |||||||||||||||||||||
Db         606 CCACCTGGCCATCGACGTGGA 626
```

```
RESULT 12
US-10-336-603A-25
; Sequence 25, Application US/10336603A
; Publication No. US20040072997A1
; GENERAL INFORMATION:
;  APPLICANT: Alsobrook et al.
;  TITLE OF INVENTION: THERAPEUTIC POLYPEPTIDES, NUCLEIC ACIDS ENCODING SAME, AND METHOD
;  FILE REFERENCE: 21402-533A
;  CURRENT APPLICATION NUMBER: US/10/336,603A
;  CURRENT FILING DATE:  2003-01-03
;  PRIOR APPLICATION NUMBER: 09/746,491
;  PRIOR FILING DATE: 2000-12-20
;  PRIOR APPLICATION NUMBER: 10/055,569
;  PRIOR FILING DATE: 2001-10-26
;  NUMBER OF SEQ ID NOS: 169
;  SOFTWARE: CuraSeqList version 0.1
; SEQ ID NO 25
;   LENGTH: 4801
;   TYPE: DNA
;   ORGANISM: Homo sapiens
;   FEATURE:
;   NAME/KEY: CDS
;   LOCATION: (178)..(3639)
US-10-336-603A-25

  Query Match             100.0%;  Score 261;  DB 12;  Length 4801;
  Best Local Similarity   100.0%;  Pred. No. 2.5e-58;
  Matches  261;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy           1 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 60
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         543 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 602

Qy          61 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 120
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         603 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 662

Qy         121 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 180
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         663 CGTGCGGCCAGTCGTGCCCTCGGCCACCGGGGAGCCCGATGGCCCTGAAGGGGAGGCGCT 722

Qy         181 GCCCGCCGCCTGCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 240
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         723 GCCCGCCGCCTGCCCCGAGGAGCTGGCCTTCGAGGCGGAGGTGGAGTACAACGGGGGCTT 782

Qy         241 CCACCTGGCCATCGACGTGGA 261
               |||||||||||||||||||||
Db         783 CCACCTGGCCATCGACGTGGA 803
```

```
RESULT 13
US-10-051-769-4
; Sequence 4, Application US/10051769
; Publication No. US20030044811A1
; GENERAL INFORMATION:
;  APPLICANT: McKINNON, Randy D.
;  TITLE OF INVENTION: AN EST-DEFINED PROBE FOR CANCER PROGRESSION
;  FILE REFERENCE: 268/260 (RWJ-00-37)
;  CURRENT APPLICATION NUMBER: US/10/051,769
;  CURRENT FILING DATE:  2001-10-20
;  PRIOR APPLICATION NUMBER: US 60/242,160
;  PRIOR FILING DATE: 2000-10-20
;  NUMBER OF SEQ ID NOS: 6
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 4
;   LENGTH: 263
;   TYPE: DNA
;   ORGANISM: Sprague Dawley rat
US-10-051-769-4

  Query Match             79.8%;  Score 208.2;  DB 15;  Length 263;
  Best Local Similarity   87.4%;  Pred. No. 1.4e-44;
  Matches  228;  Conservative    0;  Mismatches   33;  Indels    0;  Gaps    0;

Qy           1 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCGGGCGCCTGCTGGAGGG 60
               |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db           1 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGCCTTTTTTTTTTTTGGAGGG 60

Qy          61 GCTGAGCCTGCGGGACGTGTTCCTGGGCGAGACGGTGCCCTTCATCAAGACCATCCGGCT 120
               |||||||||||| |||||||||||||| || || ||||||| ||||||||||||||||||
```

Exhibit D

```
;           APPLICATION NUMBER: US 08/176,427
;           FILING DATE: 30-DEC-1993
;         ATTORNEY/AGENT INFORMATION:
;           NAME: Vincent, Matthew P.
;           REGISTRATION NUMBER: 36,709
;           REFERENCE/DOCKET NUMBER: HMI-006CP4
;         TELECOMMUNICATION INFORMATION:
;           TELEPHONE: (617) 227-7400
;           TELEFAX: (617) 227-5941
;    INFORMATION FOR SEQ ID NO: 6:
;         SEQUENCE CHARACTERISTICS:
;           LENGTH: 1425 base pairs
;           TYPE: nucleic acid
;           STRANDEDNESS: single
;           TOPOLOGY: linear
;         MOLECULE TYPE: cDNA
;         FEATURE:
;           NAME/KEY:  CDS
;           LOCATION:  1..1425
;         SEQUENCE DESCRIPTION: SEQ ID NO: 6:
US-09-736-476-6

  Query Match             8.0%;  Score 21;  DB 4;  Length 1425;
  Best Local Similarity   100.0%;  Pred. No. 0.87;
  Matches   21;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy        139 CTCGGCCACCGGGGAGCCCGA 159
              |||||||||||||||||||||
Db        837 CTCGGCCACCGGGGAGCCCGA 857
```

```
RESULT 15
US-08-748-591-5
; Sequence 5, Application US/08748591
; Patent No. 5759811
;  GENERAL INFORMATION:
;    APPLICANT:  Epstein, Ervin
;    APPLICANT:  Hu, Zhilan
;    APPLICANT:  Bonifas, Jeanette
;    TITLE OF INVENTION:  Mutant Human Hedgehog Gene
;    NUMBER OF SEQUENCES:  23
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Fish and Richardson
;      STREET:  2200 Sand Hill Road
;      CITY:  Menlo Park
;      STATE:  CA
;      COUNTRY:  USA
;      ZIP:  94025
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  PatentIn Release #1.0, Version #1.25
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/748,591
;      FILING DATE:
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  Sherwood, Pamela J
;      REGISTRATION NUMBER:  36,677
;      REFERENCE/DOCKET NUMBER:  06510/067001
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (415) 322-5070
;      TELEFAX:  (415) 854-0875
;  INFORMATION FOR SEQ ID NO:  5:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  1576 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  double
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  cDNA
US-08-748-591-5
```

```
  Query Match             8.0%;  Score 21;  DB 1;  Length 1576;
  Best Local Similarity   100.0%;  Pred. No. 0.86;
  Matches   21;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy        139 CTCGGCCACCGGGGAGCCCGA 159
              |||||||||||||||||||||
Db        988 CTCGGCCACCGGGGAGCCCGA 1008


Search completed: July 18, 2004, 15:54:55
Job time : 58 secs
```

```
LOCUS       AW013379                723 bp    mRNA    linear   EST 10-SEP-1999
DEFINITION  sp042ks Winter flounder spleen Pseudopleuronectes americanus cDNA
            clone sp042ks 5' similar to C53B4.4 [Caenorhabditis elegans], mRNA
            sequence.
ACCESSION   AW013379
VERSION     AW013379.1  GI:5862157
KEYWORDS    EST.
  SOURCE    Pseudopleuronectes americanus (winter flounder)
  ORGANISM  Pseudopleuronectes americanus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Actinopterygii; Neopterygii; Teleostei; Euteleostei; Neoteleostei;
            Acanthomorpha; Acanthopterygii; Percomorpha; Pleuronectiformes;
            Pleuronectoidei; Pleuronectidae; Pseudopleuronectes.
  REFERENCE 1  (bases 1 to 723)
  AUTHORS   Douglas,S.E., Gallant,J.W., Bullerwell,C.E., Wolff,C.,
            Munholland,J. and Reith,M.E.
  TITLE     Winter flounder expressed sequence tags: Establishment of an EST
            database and identification of novel fish genes
  JOURNAL   Marine Biotechnology (1999) In press
  COMMENT   Contact: Reith M
            Marine Biology
            NRC Institute for Marine Biosciences
            1411 Oxford St., Halifax, Nova Scotia, B3H 3Z1, Canada
            Tel: (902) 426-8276
            Fax: (902) 426-9413
            Email: michael.reith@nrc.ca
            Seq primer: M13 Forward.
  FEATURES             Location/Qualifiers
       source          1. .723
                       /organism="Pseudopleuronectes americanus"
                       /mol_type="mRNA"
                       /db_xref="taxon:8265"
                       /clone="sp042ks"
                       /sex="female"
                       /dev_stage="adult"
                       /clone_lib="Winter flounder spleen"
                       /note="Organ: spleen"
  ORIGIN

  Query Match             16.1%;  Score 42;  DB 9;  Length 723;
  Best Local Similarity   100.0%;  Pred. No. 4.2e-08;
  Matches   42;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGC 42
              |||||||||||||||||||||||||||||||||||||||||||
Db        482 GATCAAGGTGGAGTTCGAGGAGCTGCTGCAGACCAAGACGGC 523


RESULT 13
BB866050
LOCUS       BB866050                681 bp    mRNA    linear   EST 09-JUL-2003
DEFINITION  BB866050 RIKEN full-length enriched, CRL-1751 WEHI 164 cDNA Mus
            musculus cDNA clone G431003O09 5', mRNA sequence.
ACCESSION   BB866050
VERSION     BB866050.1  GI:17112260
KEYWORDS    EST.
SOURCE      Mus musculus (house mouse)
  ORGANISM  Mus musculus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
REFERENCE   1  (bases 1 to 681)
  AUTHORS   Akimura,T., Arakawa,T., Carninci,P., Furuno,M., Hanagaki,T.,
            Hayatsu,N., Hiramoto,K., Hiraoka,T., Hirozane,T., Imotani,K.,
            Ishii,Y., Ito,M., Kawai,J., Kojima,Y., Konno,H., Kouda,M.,
            Matsuyama,T., Nakamura,M., Nishi,K., Nomura,K., Numasaki,R.,
            Okazaki,Y., Okido,T., Saito,R., Sakai,C., Sakai,K., Sakazume,N.,
            Sasaki,D., Sato,K., Shibata,K., Shinagawa,A., Shiraki,T.,
            Sogabe,Y., Suzuki,H., Tagawa,A., Takahashi,F., Takaku-Akahira,S.,
            Tanaka,T., Tomaru,A., Toya,T., Watahiki,A., Yasunishi,A.,
            Muramatsu,M. and Hayashizaki,Y.
  TITLE     RIKEN Encyclopedia of Mouse Full-length cDNAs (Akimura,T., et al.
            2001)
  JOURNAL   Unpublished (2001)
  COMMENT   Contact: Yoshihide Hayashizaki
            Laboratory for Genome Exploration Research Group, RIKEN Genomic
            Sciences Center(GSC), Yokohama Institute
            The Institute of Physical and Chemical Research (RIKEN)
            1-7-22 Suehiro-cho, Tsurumi-ku, Yokohama, Kanagawa 230-0045, Japan
            Tel: 81-45-503-9222
            Fax: 81-45-503-9216
            Email: genome-res@gsc.riken.go.jp,
            URL:http://genome.gsc.riken.go.jp/
            Carninci,P., Shibata,Y., Hayatsu,N., Sugahara,Y., Shibata,K.,
            Itoh,M., Konno,H., Okazaki,Y., Muramatsu,M. and Hayashizaki,Y.
            Normalization and subtraction of cap-trapper-selected cDNAs to
            prepare full-length cDNA libraries for rapid discovery of new
            genes. Genome Res. . 10 (10), 1617-1630 (2000)
            wagi,K., Fujiwake,S., Inoue,K., Togawa,Y., Izawa,M., Ohara,E.,
            Watahiki,M., Yoneda,Y., Ishikawa,T., Ozawa,K., Tanaka,T.,
            Matsuura,S., Kawai,J., Okazaki,Y., Muramatsu,M., Inoue,Y., Kira,A.
            and Hayashizaki,Y.
            RIKEN integrated sequence analysis (RISA) system--384-format
            sequencing pipeline with 384 multicapillary sequencer. Genome Res.
            10 (11), 1757-1771 (2000)
            Konno,H., Fukunishi,T., Shibata,K., Itoh,M., Carninci,P.,
            Sugahara,Y. and Hayashizaki,Y.
            Computer-based methods for the mouse full-length cDNA
            encyclopedia: real-time sequence clustering for construction of a
            nonredundant cDNA library. Genome Res. . 11 (2), 281-289 (2001)
            Please visit our web site (http://genome.gsc.riken.go.jp) for
            further details.
            e mouse tissues.
  FEATURES             Location/Qualifiers
       source          1. .681
                       /organism="Mus musculus"
                       /mol_type="mRNA"
                       /strain="BALB/c"
                       /db_xref="taxon:10090"
                       /clone="G431003O09"
                       /cell_line="CRL-1751 WEHI 164"
                       /clone_lib="RIKEN full-length enriched, CRL-1751 WEHI 164
                       cDNA"
  ORIGIN

  Query Match             12.6%;  Score 33;  DB 10;  Length 681;
  Best Local Similarity   100.0%;  Pred. No. 0.00044;
  Matches   33;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          7 GGTGGAGTTCGAGGAGCTGCTGCAGACCAAGAC 39
              |||||||||||||||||||||||||||||||||
Db        565 GGTGGAGTTCGAGGAGCTGCTGCAGACCAAGAC 597


RESULT 14
BX369637
LOCUS       BX369637                1079 bp    mRNA    linear   EST 08-MAY-2003
DEFINITION  BX369637 Homo sapiens HELA CELLS COT 25-NORMALIZED Homo sapiens
            cDNA clone CS0DK002YA12 5-PRIME, mRNA sequence.
ACCESSION   BX369637
VERSION     BX369637.1  GI:30453826
KEYWORDS    EST.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 1079)
  AUTHORS   Li,W.B., Gruber,C., Jessee,J. and Polayes,D.
  TITLE     Full-length cDNA libraries and normalization
  JOURNAL   Unpublished (2001)
  COMMENT   Contact: Genoscope
            Genoscope - Centre National de Sequencage
            BP 191 91006 EVRY cedex - France
            Email: seqref@genoscope.cns.fr, Web : www.genoscope.cns.fr
            Library was constructed by Life Technologies, a division of
            Invitrogen. This sequence belongs to sequence cluster 5483.r For
            more information about this cluster, see
```